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Review Article

Sepsis in Old Age: Review of Human and Animal Studies

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ABSTRACT: Sepsis is a serious problem among the geriatric population as its incidence and mortality rates dramatically increase with advanced age. Despite a large number of ongoing clinical and basic research studies, there is currently no effective therapeutic strategy that rescues elderly patients with severe sepsis. Recognition of this problem is relatively low as compared to other age-associated diseases. The disparity between clinical and basic studies is a problem, and this is likely due, in part, to the fact that most laboratory animals used for sepsis research are not old while the majority of sepsis cases occur in the geriatric population. The objective of this article is to review recent epidemiological studies and clinical observations, and compare these with findings from basic laboratory studies which have used aged animals in experimental sepsis.

Key words: aging, animal models, coagulation, elderly, inflammation, sepsis

Aging is accompanied by a reduced tolerance to physiological stress, which contributes to increased vulnerability to critical illnesses in old age [1-3]. Patients over the age of 65 comprise more than half of all intensive care unit admissions in the US, and critical illnesses such as sepsis have proven to be particularly life-threatening among older patients [4]. Sepsis is the tenth leading cause of death in the elderly, defined as those ≥ 65, with both an increase in incidence and mortality compared to younger patients. Sepsis is also one of the most expensive conditions treated in US hospitals, with hospital costs exceeding $60 billion per year and a national bill which is increasing faster than for any other condition [5, 6] . Although sepsis is a serious life-threatening disease, recognition of this problem is very low compared to other age-associated diseases. Addressing this issue is urgent as the US population is rapidly aging and health care costs for the elderly are likewise expected to rise with the increasing life expectancy. The purpose of this article is to review epidemiological, clinical, and basic science data with respect to findings specific for the elderly with sepsis.

Pathophysiology of sepsis

Sepsis is a life-threatening clinical condition which involves a profound systemic response to infection and results in serious, often irreversible, damage to one's own cells and tissues [7]. Sepsis typically develops following infection that is not contained and cleared by the host. Sepsis can also develop from other diseases such as pneumonia, acute respiratory distress syndrome, and severe acute pancreatitis [8] or upon infection after burn, trauma, or surgical intervention. The most common site of infection in sepsis is the lung, but other types of infection such as genitourinary, abdominal, skin, and catheter-mediated, are also common [9-11]. Although the majority of sepsis is caused by infection with a single organism, polymicrobial sepsis also occurs frequently [10, 12]. An uncontained local infection results in progressive inflammation which becomes dysregulated and can lead

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to systemic inflammatory response syndrome (SIRS) which damages the immune system and multiple cell types. During SIRS, concentrations of multiple inflammatory cytokines in the blood are abnormally elevated [13, 14]. Cytokine production contributes to the activation of platelets and damage to vascular endothelial cells which brings about such complications as vascular leakage and disseminated intravascular coagulation (DIC). Advanced DIC can paradoxically result in bleeding as platelets and coagulation factors are exhausted [15]. These conditions often result in a feedback loop of progressive inflammation and coagulation, with a potential end result of multiple organ dysfunction syndrome and eventual death [16, 17].

The most up-to-date diagnostic criteria for sepsis include such general variables as hypo- or hyperthermia, tachycardia, tachypnea, hypotension, hyperglycemia, edema, and an altered mental status [18]. Additionally, altered inflammatory variables, including abnormal white blood cell count and elevated plasma levels of C-reactive protein (CRP) and procalcitonin, can aid in diagnoses. Arterial hypotension and abnormal levels of an array of organ dysfunction variables push the diagnosis of sepsis into a more serious state of severe sepsis (sepsis plus acute organ dysfunction) or septic shock (severe sepsis plus hypotension not reversed by fluid resuscitation). It is known that at least 60% of sepsis cases include a diagnosis of severe sepsis with organ failure [19, 20]. Additionally, elderly patients with sepsis often present with atypical symptoms which further complicates and potentially delays diagnosis [1, 21-23].

Epidemiology of sepsis

Over the years, several epidemiological studies have attempted to quantify the occurrence of sepsis in the US by reviewing nationally collected data from hospital admission and discharge records. The data presented by these studies has varied widely depending on the particular methods used for data collection. In 2001, Angus *et al.* estimated the nation-wide annual incidence of severe sepsis at 751,000 cases with an in-hospital mortality rate of 28.6% based on data derived from seven states in 1995 [9]. Noting that this study may have overestimated national numbers, Martin *et al*. undertook a larger investigation by reviewing national data over a 22-year period (1979-2000) and identified an annual incidence of sepsis (not limited to severe sepsis) ranging from about 164,000 in 1979 to 660,000 in 2000 reflecting an 8.7% annual increase in incidence [24]. The incidence of severe sepsis in this study was 184,000 in 1995 and grew to 256,000 in 2000. This study identified a decrease in mortality rate from 27.8% to 17.9% over the 22-year period, largely attributed to improvements in the intensive care setting. Despite the improved survival rates, the increasing incidence of sepsis over the years resulted in a higher number of deaths overall.

After these studies were conducted, new classification methods with specific codes for severe sepsis were employed by hospitals nationwide. Lagu *et al*. reviewed data from 2003-2007 using the new coding system and identified an annual incidence for severe sepsis ranging from 415,000 in 2003 to 712,000 in 2007 with a 17.8% increase in incidence per year and an in-hospital mortality rate of 37% in 2003 to 29% in 2007 [19]. Another recent study compared the methods used by previous epidemiological studies for nationwide data from 2004-2009 and found that the incidence of severe sepsis varied by as much as 3.5-fold depending on the method used [25]. For the year 2009, annual incidence of severe sepsis was approximately 894,000 cases by the method of Dombrovskiy *et al.* or 3,110,000 cases by the method of Martin *et al*. Mortality rates ranged from 14.7% to 29.9%. While the actual numbers varied depending on the method used, there was a clear increase in the annual incidence of severe sepsis of about 13% and a yearly increase in total mortality regardless of the method used [25]. Discrepancies in these epidemiological studies is most likely related to inclusion or exclusion of more or less sick cases; however, trends in number of cases, case fatality rate, and yearly mean increase are almost identical regardless of method used.

Sepsis in old age

Sepsis has been the tenth leading cause of death in patients over the age of 65 in the US since 2001 [26]. Older people make up a greater proportion (58-65%) of sepsis patients [9, 20, 27], and both incidence and mortality rates are significantly greater in the aged. Angus *et al.* determined that the incidence of severe sepsis increased more than 100-fold with age (0.2/1000 in children to 5.3/1000 in patients aged 60-64 years and 26.2/1000 in patients ≥85) and that mortality increased from 10% in children to 26% in patients 60-64 and 38% in those ≥85 [9]. Martin *et al.* found that the incidence of sepsis (all cases, not limited to severe sepsis) likewise increased exponentially across all adult ages with a case fatality rate of 27.7% for those >65 versus 17.7% for those <65 [27]. Dombrovskiy *et al.* reported the incidence rate of severe sepsis as 7.05-7.15/100,000 for children, 161-197/100,000 for those 50-64, 442.2-596.7/100,000 for those 65-79, and 912-1320/100,000 for those ≥ 85 for the year 2003 [20]. Notably, many elderly dying patients with infection are not documented as having "sepsis" as they often receive palliative care rather than being sent to the ICU for aggressive treatment [28].

Importantly, in addition to increased mortality rates for the elderly, older sepsis patients die earlier during hospitalization, and those that do survive often require additional care in long-term nursing facilities to regain functional status. Martin *et al* also noted that the elderly were 26% more likely to die during the first week of hospitalization for sepsis than their younger counterparts. Among elderly sepsis survivors, 76% were less likely to return home after hospital discharge, requiring continued healthcare in skilled nursing homes or non-acute health care facilities. Elderly sepsis survivors also have higher rates of comorbidites compared to younger patients [24, 29, 30], which greatly affect long-term survival after a septic insult. A recent study evaluated long-term mortality in elderly severe sepsis patients (only those surviving at three months post sepsis were included) and found an overall mortality rate of 55% with a 30.6% one-year morality rate and a 43% two-year mortality rate [31]. This means that more than half of the elderly patients who survive sepsis through hospital discharge will be dead within two years. The authors noted that congestive heart failure, peripheral vascular disease, dementia, and diabetes were most associated with long-term mortality in the elderly post-sepsis.

Unique pathophysiology of sepsis in the elderly

Dysfunctional Immune System

Both the innate immune response and adaptive immune response are dysregulated by aging, which largely contributes to the increased incidence of infection in the elderly [32-36]. A defective adaptive immune response has long been attributed as the cause for decreased immune function in old-age; however, studies within the last decade indicate multiple age-related changes to cells of the innate immune system are to blame as well [37]. Within the adaptive immune system, B cell number and generation of naïve T cells is decreased by aging, which collectively results in a diminished ability to rapidly respond to new pathogens [38]; however, the ability to initiate an efficient response to previously encountered pathogens remains intact [3]. Within the innate immune system, although cell numbers appear preserved in old-age, both neutrophils and macrophages exhibit age-related functional alteration, including reduced chemotaxis, phagocytosis, antibacterial defense, and generation of reactive oxygen species (ROS) [39].

Altered Cytokine Production

While older age is clearly associated with chronic elevation of proinflammatory cytokines [40-42], there is debate about whether sepsis-induced cytokine alterations are age-specific. Severe sepsis and mortality are associated with higher levels of pro-inflammatory markers; however, few clinical studies have compared sepsis-induced cytokine responses in young and elderly patients [2]. Kale *et al.* recently reported no age-related difference in inflammatory markers IL-6, TNFα, or IL-10 at admission or over the first week of hospitalization in sepsis patients with community-acquired pneumonia; however, IL-6 levels at discharge were significantly higher in the elderly suggesting an age-dependent delay in resolution of inflammation [43]. IL-6 levels at discharge have also been found to predict all-cause mortality in elderly patients with sepsis of different etiologies [44]. Another study noted no difference in IL-6 levels at admission across various ages in patients with septic shock, but higher levels of TNFα in patients ≥85 was noted [45]. Bruunsgaard *et al.* reported no age-related difference in IL-1β, IL-6, TNFα, or IL-10 on admission in patients hospitalized with *Streptococcoccus pneumonia* infection; however, on Day 7 of hospitalization, elderly patients had significantly higher levels of TNFα compared to younger patients, again suggesting a prolonged inflammatory response in the aged [46]. The levels of soluble adhesion molecules, markers of inflammation, were also noted to be significantly increased in elderly, compared to younger, ICU patients with sepsis secondary to post-operative complications [47]. This study further noted that while adhesion molecule levels in young patients resolved to normal with five days, concentrations in elderly patients remained high throughout the study.

Coagulation Abnormalities

Coagulation abnormalities, particularly a prothrombotic state, are abound during sepsis. While the tendency to develop DIC and exaggerated levels of various coagulation-related factors are fairly well characterized in sepsis patients [15, 48, 49], little is known about age-associated differences in expression of thrombotic genes and how these relate to clinical outcome [2]. Additionally, while advancing age is associated with heightened coagulation [40, 50], the propensity for this chronic condition to worsen coagulation during sepsis is unknown [2]. The above mentioned study by Kale *et al.* also evaluated thrombosis markers in sepsis patients with community-acquired pneumonia and found a modest age-related increase in levels of d-dimer and TAT and a modest age-related decrease in levels of plasminogen activator inhibitor 1 (PAI-1), anti-thrombin (AT), and factor IX, which occurred at admission and persisted through discharge [43]. However, this study noted that these modest changes were unlikely to account for the drastic difference in mortality between young and old

patients and suggested that the elderly may have a more exaggerated response to similar levels of inflammatory and thrombotic factors which influences the development of organ dysfunction. Kale *et al.* also suggested that investigations at the tissue level may reveal stronger age-dependent associations. While data is lacking on levels of these prothrombotic factors in elderly versus young sepsis patients of different etiologies, clinical trials with activated protein C (an endogenous anticoagulant molecule) in severe sepsis showed that the efficacy was greatest in elderly patients [29, 51], suggesting heightened thrombosis in old age.

The significance of animal research on sepsis

Sepsis patients, in addition to being a heterogeneous population, have large variations in disease course factors including severity, source of infection, comorbidities, and timing of hospital admission. While caution has to be paid for biological differences between men and rodents [52], the use of laboratory animals is essential for understanding the detailed pathophysiology of sepsis. Animal studies enable us to induce sepsis with specific sources of infection (pneumonia, peritonitis, kidney or urinary infections, bacteremia, etc.) and perform multiple histological and biochemical analyses on various tissues at desired time-points. Additionally, manipulation of gene expression (by gene knockout, transgene, or RNAi) in rodents allows for the characterization of gene function, and the efficacy of therapeutic intervention can be easily tested in animal models of sepsis.

Use of Aged Animals for Sepsis Research

Despite the fact that there is clearly an increased precedence of elderly patients suffering from sepsis, the majority of basic research on sepsis has been conducted using young animals [53]. This mismatch introduces a serious disconnect in interpretation of sepsis studies using mice or men because most humans with sepsis are over 50 years old, and most mice used in sepsis research are less than 3 months old, comparable to a person under 20 years of age [53-56]. For example, immune responses to infection are clearly altered by aging [57, 58], thus, the use of aged animals in sepsis research would provide important information that would greatly differ from data obtained using young animals. The number of studies on sepsis using aged animals (i.e. rodents) is surprisingly small. By utilizing the PubMed journal search engine, we estimate that among all published studies using animal models of sepsis, less than 1% used appropriately aged animals.

Because of their relatively short lifespan and commercial availability, mice and rats have been used almost exclusively as animal models to investigate sepsis at advanced age. Most of the widely used inbred strains of mice and rats have a 2-3 year mean lifespan if given good care and a regular diet [59]. However, aging speed is not the same among rodent strains, and caution must be taken to choose appropriate ages. For male C57BL/6 mice in which 26 months is the age at which 50% of the population naturally survive (in the laboratory setting), 3-6 months old represents a mature adult (20-30 in human years), 10-14 months old represents middle-aged (36-47 in human years), and 18-24 months old represents old mice (56-69 in human years) [54]. Our laboratory, for example, mainly uses 4-5 month old, 12-14 month old, and 23-26 month old mice of the C57BL/6 strain for young, middle-aged, and aged mouse groups, respectively [60-67]. The use of very young mice (before complete sexual maturation) as young controls for aged mice is not preferable as these mice are still developing. Inclusion of very old mice (>26 months) is sometimes desirable, but mice in this group often exhibit large variations such as frailty status and tumor burden or are exceptionally long-living. Many published studies have assessed "the effects of aging" on sepsis pathophysiology by comparing pediatric ages with young-adult animals. Since these studies are more appropriate for investigating neonatal sepsis, they are not included in this review. Likewise, studies on middle-aged rodents without adequate old-age are also not included in this review.

Animal models of sepsis

To study sepsis (or a sepsis-like condition) in aged rodents, investigators use various methods which cause: 1) polymicrobial peritonitis sepsis by cecal ligation and puncture (CLP), 2) endotoxemia by injection with lipopolysaccharide (LPS), 3) bacteremia by injection with a known strain of bacteria, 4) pneumonia by intranasal or intratracheal administration of bacteria or endotoxin, and 5) acute pancreatitis by chemical injection. Among these, CLP is currently regarded as the most widely accepted model mimicking a clinically relevant septic condition; however, because polymicrobial peritonitis is not the most common type of infection in sepsis, these other models are also important.

In the CLP model, polymicrobial peritonitis is induced by surgical ligation of the cecum followed by needle puncture to secrete cecal contents into the peritoneal cavity [68, 69]. Although variation in mortality rate is quite large among different laboratories, the severity of sepsis can be well controlled [70]. Another widely used model is LPS-induced endotoxemia in which intraperitoneal or intravenous injection with gram negative bacterial endotoxin LPS elicits acute sterile SIRS. Since LPS alone is not infectious, this model is not

applicable for studying bacterial clearance. Despite the lack of clinical relevance to infection-initiated sepsis, the LPS model has been widely used for SIRS research due to its simplicity (administration without anesthesia and surgery) and its dose-dependent controllable nature. The LPS model has a few advantages over CLP in studies when the effects of surgery are problematic or when comparing animals with different cecum size or cecal content consistency. Bacteremia models, with either intraperitoneal or intravenous injection of live bacteria, circumvent the problems of the sterile LPS model though reproducibility can be compromised due to variations in bacterial preparation. It is also a concern that both LPS and bacteremia models elicit extremely rapid immune responses which are usually not observed clinically. The remaining models (pneumonia and acute pancreatitis) are designed to address specific types of sepsis or SIRS. Each of the models has certain advantages and disadvantages; thus, there is no single ideal model for sepsis [55]. The choice of model should depend on the research question addressed in each study.

Pathophysiology of aged rodents during experimental sepsis

Mortality in Aged Animals

Mortality rates in aged animals compared to young have been reported using various sepsis models. With CLP, two published studies have shown significantly higher mortality rates in aged mice [62, 71]. While these studies used C57BL/6 mice, a similar result was subsequently confirmed in the FVB strain of mice [72]. However, a more recent study, using a model of trauma/hemorrhage followed by CLP, observed a survival advantage in female over male mice without significant difference by aging [73]. With LPS, a larger number of published studies found an age-dependent increase in mortality regardless of sex or strain using mice [62, 66, 74-77] and rats [78]. Age-dependent mortality was also recently shown in a model of acute pancreatitis-induced SIRS [60].

An early study using a bacterial infection model with outbred NMRI mice found significantly increased mortality in the aged compared to the young after injection with *Salmonella typhimurium* but not *Listeria monocytogenes* [79]. However, another study with *L. monocytogenes* observed increased mortality in aged AB6F1 mice compared to middle-aged mice [80]. F344 rats injected with *S. typhimurium* showed no age-associated difference in mortality [81]. These inconsistent results may be partly due to the same dose of inoculation in young and aged animals despite a significant difference (>2-fold) in body size [81]. Additional studies showed a marked increase in mortality by aging using intravenously injected *Staphylococcous aureus* in DBA and CF1 mice [82] and intravenously injected *Mycobacterium tuberculosis* to AB6F1 mice [83]. An age-related increase in mortality was also shown in a recent study using a novel model of sepsis-induced acute kidney injury in mice by uterine ligation followed by *E. coli* inoculation [84].

Studies with pneumonia models of intranasal infection have given mixed results with regard to age-associated mortality. Antonini *et al.* demonstrated increased mortality and lung lesions in aged F344 rats as compared to young after inoculation with *L. monocytogenes* [85]. A study with *Francisella novicida* showed 100% mortality in young C57BL/6 mice while 20% of aged mice survived with increased control of bacterial replication [86]. An earlier study with *Staphylococcus aureus* and *Klebsiella pneumonae* infection found identical lethality in young and aged C57BL/6 mice with more rapid bacterial clearance in the aged [87]. On the other hand, a study on Balb/c mice with *Chlamydophila pneumonae* showed an age-associated reduction in bacterial clearance [88]. A more recent study on *Streptococcus pneumoniae* infection found increased pulmonary inflammatory response by aging but mortality rates were again not significantly different in young versus aged mice [89]. Since severity of systemic inflammation was not assessed in some of these studies, it is not clear whether animal death resulted from sepsis or local pulmonary injury alone. This wide variability in results may be due to different bacterial strains, host animal strains, animal breathing pattern, or inoculation techniques. In the case of intranasal administration, distribution of instilled substances is significantly affected by the volume of instillation and presence of anesthesia [90].

With the exception of bacterial pneumonia models, an age-dependent increase in mortality has been confirmed in the majority of studies that performed survival tests in aged vs. young-adult rodents using different experimental models of sepsis, including polymicrobial peritonitis by CLP, endotoxemia by LPS, systemic bacteremia, and acute pancreatitis.

Inflammatory Response in Aged Animals

Compared to young animals, aged animals exhibit augmented inflammatory responses under both sepsis and sterile sepsis-like conditions. Concentrations of various inflammatory cytokines in the circulation, which are usually increased during sepsis, are often higher in aged animals compared to young when given the same insult. These include TNFα [60, 64, 71, 76, 77, 91, 92], IL-1α [77], IL-1β [62], IL-6 [60, 62, 64, 77, 92-94], IL-10 [62, 77], HMGB-1 [95] and leptin [64]. It is noteworthy that in

addition to augmented expression of pro-inflammatory cytokines, anti-inflammatory IL-10 is also augmented in the aged, indicating an overall enhancement of the sepsis-induced systemic inflammatory response by aging. Some studies measured mRNA levels of these inflammatory factors in tissues and demonstrated that gene expression of these factors are also augmented by aging. Examples include IL-6 in the heart and lung [61, 62] and kidney, spleen, and adipose tissues [63, 64], IL-10 in the heart and lungs [62], IL-1α and β in visceral fat [64], and ICAM-1 in the heart [61]. Induction of inducible nitric oxide synthase (iNOS) mRNA is also dramatically augmented in the lungs of aged mice compared to young during endotoxemia [67]; this data corroborates an earlier study showing an age-associated increase in plasma NO levels [76]. Augmented cytokine gene expression is not always due to increased peak levels of mRNA induction, but rather a prolonged induction of gene expression with age [61]. Delayed resolution of the inflammatory response found in this study on aged mice fits well to the clinical observation that elderly patients showed significantly elevated IL-6 levels at hospital discharge [43].

It is debatable whether elevated cytokine levels in aged animals contribute to mortality. For instance, while elevated plasma IL-6 levels in the early phase of sepsis is highly regarded as a biomarker for predicting later death [96], young IL-6 null mice showed the same mortality rates as wild-type control mice after CLP [97]. Another study showed that young IL-6 null mice are more sensitive to endotoxemia [98], suggesting a protective role for this cytokine during sepsis. This may be partly explained by a negative feedback mechanism in which IL-6 suppresses its own inducers TNFα and IL-1β [99, 100]. However, old IL-6 null mice are more resistant to endotoxemia than their wild-type counterparts, suggesting that augmented expression of this cytokine is harmful during systemic inflammation in old age [63, 74]. Furthermore, animals with sepsis can be rescued by partial blockage of IL-6 with an antibody [101]. Generally, it would be reasonable to speculate that well-regulated modest induction of inflammatory cytokines (as noted in surviving young animals) is biologically programmed as a host defense mechanism whereas uncontrolled overproduction of cytokines, often seen in aged animals with sepsis, can be harmful and contributes to the age-associated mortality [62, 63].

Hypothermia in Aged Animals

Compared to young mice, more profound hypothermia is observed in aged mice after both CLP surgery and LPS injection [62, 75]. The severity of hypothermia during the early phase correlated well with plasma IL-6 levels and later mortality [62]. A study on young IL-6 null mutant mice showed decreased severity of hypothermia during CLP-induced sepsis indicating the importance of this cytokine for regulating body temperature [97]. A significant association between sepsis-related hypothermia and fatal outcome is well known [102]. A recent clinical study confirmed that hypothermia during the first 24 hours of presentation independently predicts hospital mortality among elderly patients with sepsis [103]. However, results from a recent Norwegian study indicate that incidence of hypothermia during sepsis is not increased with advanced age [21].

Cell Death and Tissue Damage in Aged Animals

Histologic changes under systemic inflammation are often more prominent in aged animals compared to their young counterparts. Age-associated enhancement of inflammatory cell infiltration, edema, and/or cell death in the lung, liver, and kidney has been reported in mouse models of endotoxemia [67, 104, 105] and acute pancreatitis [60]. Age-associated profound down-regulation of extracellular superoxide dismutase (EC-SOD), the only known extracellular anti-oxidant enzyme, is known to contribute to increased tissue damage in aged mice during systemic inflammation [67]. Microvascular endothelial cells from aged rats, compared to cells from young rats, were also shown to be more sensitive to oxidative stress and cellular damage induced by inflammatory factors present in sera from septic patients [106]. Splenic and gut epithelial apoptosis after CLP is more frequently seen in aged mice than young mice [107]. It is well documented that human septic patients exhibit lymphocyte and intestinal epithelial cell apoptosis [108] and that the former is associated with a poor outcome [109, 110]. Whether or not these sepsis-induced changes also occur in humans with advanced age is currently unknown.

Coagulation in Aged Animals

Aging alone is accompanied with an increased pro-thrombotic state [111, 112]. Abnormally enhanced coagulation is also often seen in aged but not young animals during sepsis. One study found that LPS-induced induction of PAI-1is augmented in aged mice, which is causally associated with suppressed fibrinolysis and increased thrombosis [113]. Another study demonstrated that activation of anti-coagulant factor protein C (PC) is strongly suppressed in aged mice with endotoxemia, resulting in increased coagulation with aging [66]. Taken together, two major anti-coagulant mechanisms, fibrinolysis and the protein C pathway, are suppressed in aged animals during systemic inflammation. Age-dependent disseminated intravascular coagulation in the

lung and kidney, and increased plasma levels of PAI-1 were also recently demonstrated in a murine acute pancreatitis model [60]. Additionally, pro-coagulant factors including tissue factor, thrombospondin-1, PAI-1, and PAI-2 are strongly expressed in visceral white adipose tissues in an age-dependent fashion during systemic inflammation, suggesting an important role of white fat in sepsis pathophysiology [64].

Sepsis Pathophysiology Specific to Aging

The finding of a specific pathophysiology that is exaggerated in aged but not young animals with sepsis is of great interest as such may be a direct cause of increased mortality to sepsis in the aged. However, because mortality from sepsis itself is increased by aging, a certain aspect of sepsis pathophysiology that appears to be enhanced in an age-associated fashion may not be a direct age-dependent phenomenon but rather a reflection of increased severity of disease. In fact, most factors of the sepsis pathophysiology index are likely to be more prominent in experimental animal groups with higher mortality rates making it difficult to identify what changes are exaggerated by aging and thus contribute to increased mortality. Only a few studies have addressed this problem to date. One such study [72] compared immune-pathologic responses after CLP in three groups: young mice with a minor injury (one puncture with 30-gauge needle resulting in 73% survival in 1 week), young mice with a severe injury (double puncture with 25-gauge needle resulting in 51% survival in 1 week), and aged mice with a minor injury (one puncture with 30-gauge needle resulting in 35% survival in 1 week). While experiments comparing young and aged mice with a similar injury but significantly higher mortality rates in the aged also showed an age-associated increase in plasma cytokine levels and splenic apoptosis frequency, none of these factors showed age-associated significance when young mice were given a more severe injury to replicate the mortality rate equivalent to aged mice. Thus, despite a correlation between mortality and increased plasma cytokine levels and splenic apoptosis frequency in aged mice, the authors concluded that systemic processes culminating in death may be age-independent. It is intriguing that the same study found that local peritoneal cytokine production seems to be exaggerated in an age-dependent fashion regardless of mortality.

Another study [66] induced endotoxemia by LPS and compared mortality, degree of hypothermia and thrombosis in three animal groups; young mice with a low dose of LPS (2.5 mg/kg resulting in no mortality in 1 week), young mice with a higher dose of LPS (20 mg/kg resulting in 78% mortality in 1 week), and aged mice with the same low dose of LPS (2.5 mg/kg resulting in 80% mortality in 1 week). The aged mice (given low LPS dose) and young mice given high LPS dose showed almost identical mortality rates and degrees of hypothermia, which were both significantly higher than in young mice with low LPS dose, suggesting that profound hypothermia under systemic inflammation is dependent on the severity of disease, rather than age. However, systemic coagulation in the lung, kidney, and liver was significantly exaggerated only in aged mice but not in either of the young mouse groups (those with high LPS dose and similar mortality rate or those with low dose LPS and no mortality). The same study further reported that aged mice under systemic inflammation exhibit abnormally low levels of activated protein C (aPC) which appears to be causally linked to the age-dependent exaggeration of thrombosis. These experiments were subsequently confirmed in experimental abdominal sepsis induced by CLP (unpublished data, manuscript in preparation). These results suggest a possible age-dependent increase in DIC resulting from low aPC during sepsis, which supports results from a clinical trial that showed a higher efficacy of recombinant aPC in elderly sepsis patients [29, 51].

Concluding remarks

The incidence of sepsis increases exponentially from childhood to geriatric age with a magnitude of approximately 100-times. Mortality from sepsis also increases progressively with age. Older sepsis survivors suffer long-term dysfunction with high mortality rates even after being discharged from the hospital. The incidence of sepsis is steadily increasing as our population ages. Despite these problems, little is known about the pathophysiology of sepsis which is specific to older patients. Studies using various animal models of sepsis have identified that mortality, inflammation, hypothermia, apoptosis, and coagulation (DIC) are increased in aged compared to young animals. Among these, degrees of systemic inflammation, hypothermia, and apoptosis appear to be age-independent if adjusted by mortality rates. Altered coagulation and local inflammation during sepsis, on the other hand, may be a direct result of patient age. While these interesting animal findings may shed light on the pathophysiology of sepsis specific to older patients, many have yet to be confirmed in clinical studies.

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